PB80-162852

# Air Pollution, Airways Hyperreactivity, and Pulmonary Function Measurements in Asthma

National Jewish Hospital and Research Center
Denver, CO

Prepared for

Environmental Protection Agency, Denver, CO
Region VIII

Oct 77

U.S. Department of Commerce
National Technical Information Service
NTIS.

PB80-162852

EPA-908/1-77-004

# AIR POLLUTION, AIRWAYS HYPERREACTIVITY, AND PULMONARY FUNCTION MEASUREMENTS IN ASTHMA

by

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Environmental Protection Agency Contract No.
68-02-2517

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| | |
|---|---|
| 1. REPORT NO. EPA-908/1-77-004 | 2. reactivity! |
| 3. RECIPIENT'S ACCESSION NO. PB 80 162852 | |
| 4. TITLE AND SUBTITLE AIR POLLUTION, AIRWAYS HYPERSENSITIVITY, AND PULMONARY FUNCTION MEASUREMENTS IN ASTHMA | 5. REPORT DATE October, 1977 |
| | 6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) Sheldon L. Spector, Robert A. Kinsman, Melissa Dunning | 8. PERFORMING ORGANIZATION REPORT NO. |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS National Jewish Hospital and Research Center 3800 East Colfax Denver, CO 80206 | 10. PROGRAM ELEMENT NO. |
| | 11. CONTRACT/GRANT NO. 68-02-2517 |
| 12. SPONSORING AGENCY NAME AND ADDRESS Office of Air Programs U.S. Environmental Protection Agency 1860 Lincoln Street Denver, CO 80295 | 13. TYPE OF REPORT AND PERIOD COVERED |
| | 14. SPONSORING AGENCY CODE |

15. SUPPLEMENTARY NOTES

16. ABSTRACT

This study evaluated the relationship between spirometric pulmonary function measures and air pollution and meterologic variables for adult asthmatic in-patients in an urban, long-term intensive treatment center.
Two groups of 67 patients were studied during a late spring-summer period and a late fall-winter period. Patients were classified according to the role of allergic factors and the degree of airways hyperreactivity. In all analyses, 24-hour average levels of air pollution preceding pulmonary function measurement were related to subsequent 8:00AM pulmonary functions. Multiple linear regression analyses by leaps and bounds for individuals and groups, defined by reaginic factors and airways hyperreactivity, failed to identify a systematic effect for any air pollution variable upon any pulmonary function measure. The lack of any relationship does not appear attributable to limited exposure to air pollution variables, but may be affected by as-needed (PRN) medication usage, type of pulmonary function measurement employed, and periods selected for analyses. The relative strengths and limitations of the study are discussed.

17. KEY WORDS AND DOCUMENT ANALYSIS

| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
|---|---|---|
| Air pollution<br>Human health<br>Lung diseases<br>Asthma | Denver, CO | |

| 18. DISTRIBUTION STATEMENT | 19. SECURITY CLASS *(This Report)* | 21. NO. OF PAGES |
|---|---|---|
| Distribution unlimited | unclassified | |
| | 20. SECURITY CLASS *(This page)* unclassified | 22. PRICE |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

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## ACKNOWLEDGEMENT

We gratefully acknowledge the statistical assistance of Helen Rose, and the assistance of Sharon Robinson and Jolene Fukuhara during various aspects of the study. Carolyn Wangaard and Cynthia Westmoreland dedicated considerable time assembling large amounts of medical information for the patients studied.

The Colorado Department of Health Air Pollution Surveillance Section cooperated consistently throughout this project, providing technical advice and all daily air pollution data for the study. We particularly appreciate the cooperation of Mr. Robert D. Siek, Assistant Director for Environmental Affairs, and Dave Rose and Steve Arnold, Senior Air Pollution Specialists from that office.

Indoor-outdoor air pollution monitoring was provided by Pedco Environmental Specialists, Inc. of Cincinnati, Ohio working under EPA contract No. 68-02-2294. Larry Elfers of Pedco supervised this work and S. David Shearer, Director of the Environmental Monitoring and Support Laboratory of EPA facilitated cooperation between these projects.

Finally, the Department of Biometrics of the University of Colorado Medical Center, headed by Dr. Strother Walker, provided invaluable statistical expertise for the analyses of the data.

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## 1. ABSTRACT

This study evaluated the relationship between spirometric pulmonary function measures ($FEV_1$, $FEV_1/FVC\%$, and PEFR) and air pollution and meterologic variables (CO, $SO_2$, total hydrocarbons, $O_3$, coefficient of haze, minimum temperature, and barometric pressure)for adult asthmatic inpatients in an urban, long-term intensive treatment center.

Two groups of 67 patients were studied during a late spring-summer (May 1 through August 12, 1975) and a late fall-winter (November 15, 1975 through March 31, 1975) period. Patients were classified according to the role of allergic factors and the degree of airways hyperreactivity.

In all analyses, 24-hour average levels of air pollution preceding pulmonary function measurement were related to subsequent 8:00 am pulmonary functions. Multiple linear regression analyses by leaps and bounds for individuals and groups, defined by reaginic factors and airways hyperreactivity, failed to identify a systematic effect for any air pollution variable upon any pulmonary function measure. The lack of any relationship does not appear attributable to limited exposure to air pollution variables, but may be affected by as-needed (PRN) medication usage, type of pulmonary function measurement employed, and periods selected for analyses. The relative strengths and limitations of the study are discussed.

This report was submitted in fulfillment of Contract No. 68-02-2517 by National Jewish Hospital and Research Center under the sponsorship of the U.S. Environmental Protection Agency. This report describes work completed during the contract period September 1, 1976 to March 1, 1977.

## 2. INTRODUCTION

Air pollution has often been implicated in aggravating respiratory illness, but its effect upon asthmatic patients may be particularly significant due to the hyperreactivity of their airways. Airways hyperreactivity has been regarded as among the definitive features of asthma, predisposing these patients to react to a wide range of known irritants with increased airway obstruction.[1,2] Histamine and methacholine inhalation challenges enable differentiation of asthmatics from patients who wheeze due to other causes, and permit classification of patients according to the degree of airways hyperreactivity.[3-5] The degree of airways hyperreactivity has been related to exercise-induced asthma,[6,7] amount of oral corticosteroids prescribed at discharge from long-term treatment,[4] and the response to bronchoconstrictive suggestion.[8] Likewise, those patients with the most hyperreactive airways may be affected most by irritant air pollution variables (e.g., $SO_2$ and $O_3$).

There is a considerable literature on the effects of air pollution upon respiratory illness. Many early studies have been epidemiologic, enumerating clinic and hospital visits and morbidity during periods of significant urban air pollution.[9-12] These epidemiological studies have often made retrospective determinations of the incidence of respiratory illness and lack precise information about the types of patients affected, but they have generally agreed that increased clinic and hospital visits and morbidity are associated with episodes of heightened urban air pollution.[9-12] In contrast, Greenberg, et al. found no increase in difficulties among asthmatics (as indexed by clinic and hospital visits and morbidity) in New York City for a high pollution period in the fall of 1952 during which the observed increase in air pollution levels could not be related to pollens, $SO_2$, COH, or CO.[13] Such negative findings may sometimes result from the mode of analyses. For example, Ribon, Glasser, and Sudhivoraseth[14] observed no increase in medical visits and morbidity during a period of high air pollution in New York City. However, they related clinic and office visits to air pollution levels on the <u>same</u> day and thereby may have failed to allow for the delay in symptom appearance and the subsequent decision or need to seek treatment. Lawther and Waller[15,16] have noted that the physiological response to air pollution may lag, exacerbating bronchitis only after a period of relatively prolonged exposure to high levels of urban smog.

Increased medical visits have also been associated with periods of low temperatures or decreases in temperature.[17-19] Laboratory studies with asthmatic patients have suggested that inhalation of cold air, and not mere cold exposure, results in increased airway resistance.[20] Additionally, Salvaggio and his colleagues have suggested that seasonal factors, such as low temperatures and airborne pollens, may lead to increased asthma attack rates in New Orleans, an effect easily misattributable to increased levels of air pollutants.[21]

More recently, prospective studies in Salt Lake City and New York City have measured the effect of specific pollutants (notably $SO_2$, particulates, and suspended sulfates) on the reports of asthma attacks within preselected groups of asthmatic patients.[22, 23] In these studies, increased asthma attack rates were associated with cooler temperatures, increased suspended particulates, and sulfates. Surprisingly, cooler temperatures did not increase the impact of air pollution levels in either study, but instead the effect of sulfates and particulates were more pronounced on warmer than cooler days. Since both air pollutants and temperature appear to affect asthma attacks, this apparent paradox may be due to decreased outdoor exposure on cold days. For both studies, $SO_2$ levels were not clearly related to attack rates. However, when a major plant producing $SO_2$ in Salt Lake City was closed during a strike, $SO_2$ levels decreased abruptly and were accompanied by a pronounced decrease in the asthma attack rates.[22] These observations agree with those of others that $SO_2$ appears to contribute to bronchoconstriction among individuals with hyperreactive airways.[24, 25]

Systematic studies such as these have produced the clearest findings about asthmatic symptoms and air pollution. However, neither study controlled for the seasonal effect of airborne pollens, which alone could exacerbate symptoms for patients with an allergic (i.e., reaginic) component to their asthma.[21, 25] Furthermore, objective pulmonary functions have not yet been related to air pollutants for a well-defined group of asthmatics with documented airways hyperreactivity. The need for objective measurement is emphasized by studies of subjective symptomatology in asthma,[26, 27] which document the variety of ways asthmatic patients report their distress.

As a preliminary project, this proposed study attempted to contribute useful information by (1) using a well-defined asthmatic population, (2) classifying patients according to the role of reaginic factors and airways hyperreactivity, (3) considering the effect of temperature and barometric pressure in all analyses, (4) using daily spirometric pulmonary functions as objective measures of airway obstruction, and (5) minimizing the influence of airborne pollens by studying separately nonallergic asthmatics as determined by skin testing and antigen inhalation challenges.[3-5]

## 3. METHODS

### 3.1 PERIODS OF STUDY

Asthmatic inpatients were studied throughout two periods, May 1 through August 12, 1975 (spring-summer) and November 15, 1975 through March 31, 1976 (fall-winter). For both periods, daily 8:00 a.m. spirometric pulmonary functions and medications were available for all patients throughout treatment.[28] These periods were selected to maximize the range and variability of air pollution and meterologic variables. The principal variable of interest during the late spring-summer period was ozone ($O_3$), which achieves its maximum levels during summer.[29] Levels of all other air pollutants are highest during the late fall-winter period, while lower temperatures also occur during this period. During both periods, 67 patients were in residence at the hospital for continuous periods of not less than two weeks. In addition,

these patients included only those without significant gaps in their pulmonary function data.

## 3.2 PATIENT CHARACTERISTICS

The patients were well-defined groups of 67 asthmatics for both the summer and winter periods admitted to the intensive long-term treatment program at National Jewish Hospital and Research Center (NJHRC) in Denver, Colorado. Patients within periods were comparable with respect to age (mean ±SD: 36 ± 16 and 40 ± 16, for summer and winter respectively) and sex (46 females and 48 females). Reaginic factors, identified by skin testing and antigen inhalation challenges, were determined to be involved in the asthma of 37 patients for the summer and 26 patients for the winter period.[5,30] Tests for airways hyperreactivity were available for all patients during the summer and 60 patients during the winter period. Of these, with the exception of 4 patients during summer and 3 during winter, all had hyperreactive airways as determined by methacholine and histamine inhalation challenges.[3-5] Experience with these patients has indicated that nearly all (86%) could be expected to have asthma exacerbated by infection.[31]

Skin testing and/or antigen inhalation challenges were available for 62 patients during the summer and 63 patients during the winter period. Since only patients with asthma mediated by allergic (i.e., reaginic) factors should be affected by increased airborne allergens, all analyses were performed within groups of patients classified according to the role of reaginic factors in their asthma. Specifically, patients were categorized into three groups: (A) reaginic asthma, as determined by skin testing and antigen inhalation challenges (summer: 14 patients, winter: 3 patients); (B) possibly reaginic asthma, as determined by skin test results alone (summer: 23 patients; winter: 23 patients); and (C) not reaginic asthma (summer: 25 patients, winter: 37 patients). Testing was unavailable for 5 patients during summer and 4 patients during the winter period; these patients were treated separately in all subsequent analyses.

## 3.3 MEASURES

### 3.3.1 Air Pollution and Meterologic Variables

All air pollution variables were monitored at the Colorado Department of Health Air Pollution Surveillance Substation located on the hospital grounds. This substation was approximately 100 yards from the Andrew Goodman Building where the adult asthmatic patients resided during treatment. Two weather variables were also available on a daily basis: 8:00 am barometric pressure, obtained from the NJHRC Pulmonary Function Laboratory and temperature (daily average and minimum) obtained from two substations, Overland Park Golf Course and Welby, approximately two miles southwest and northwest of NJHRC, respectively. Therefore, average values from both substations were used.

In summary, the air pollution and meterologic variables studied were:

| Measure | Source | Units |
|---|---|---|
| 1. Coefficient of haze (COH) | NJHRC Substation | COHs/1000 feet |
| 2. Carbon Monoxide (CO) | NJHRC Substation | parts per million (ppm) |
| 3. Sulfur Dioxide ($SO_2$) | NJHRC Substation | parts per million (ppm) |
| 4. Total Hydrocarbons (THC) | NJHRC Substation | parts per million (ppm) |
| 5. Ozone ($O_3$) | NJHRC Substation | parts per million (ppm) |
| 6. Minimum Temperature | $\frac{\text{Welby + Overland}}{2}$ | degrees celsius ($C^o$) |
| 7. Barometric Pressure (BP) (8:00 am) | NJHRC | mm of mercury (mmHg) |

For coefficient of haze (COH), measurements were taken every two hours. For all other air pollution variables, hourly measurements were available. An initial step in data preparation involved calculating the mean level of the air pollution variables for the 24-hour period preceding 8:00 am pulmonary function measurement. For temperature, the average and minimum values (Tmin) for the same 24-hour period were used. The objective was to capture any cumulative effect of air pollution for the 24-hour period immediately preceding pulmonary function measurement.

### 3.3.2 Pulmonary Function Measurements

For all patients, spirometric pulmonary function measurements (Vertek 5000 VF Lung Function Analyzer; Hewlett-Packard, Boston, Mass.; calibrated biweekly with a 1.5 liter syringe) were obtained twice daily (8:00 am and 4:00 pm) throughout treatment. These measurements, which provide objective indices of airway obstruction, include Forced Vital Capacity (FVC), measuring the volume of air (liters) expired forcefully following a full inspiration; First Second Forced Expiratory Volume ($FEV_1$), measuring the volume of air (liters) expired during the first second of FVC; and Peak Expiratory Flow Rate (PEFR), measuring the maximum flow rate (liters/sec) attained during FVC. Of these, $FEV_1$ and PEFR are used as indices of airway obstruction.

As an additional index, $FEV_1$ was expressed as a percentage of FVC ($FEV_1/FVC\%$). Normal values of $FEV_1/FVC\%$ are generally between 75% to 85%, indicating that this percentage of FVC is expired during the first second. As airways obstruction increases, the decrease in the diameter of the airways serves to reduce $FEV_1/FVC\%$, while FVC may remain unaffected. All pulmonary function measurements, summarized below, were based on at least two reproducible determinations to insure stable and reliable measures for each occasion:

| Measure | Units |
|---|---|
| 1. First Second Forced Expiratory Volume ($FEV_1$) | Liters |
| 2. $FEV_1$ as a percentage of Forced Expiratory Volume (FVC) ($FEV_1/FVC\%$) | Percent |
| 3. Peak Expiratory Flow Rate (PEFR) | Liters/Second |

On a daily basis, all measurements are verified and added to the computer files of the Clinical Data Management System (CDMS) and subsequently available for retrieval.

### 3.3.3 Indices of Airways Hyperreactivity

Airways hyperreactivity was indexed by histamine and methacholine inhalation challenges, performed following the recommendation of the National Institute of Allergy and Infectious Disease panel on Standardization of Bronchial Inhalation Challenge Procedures.[30]

Patients were asymptomatic at the time of the methacholine challenges as indicated by baseline $FEV_1$s of 80% or greater of the highest previously observed value. Three minutes following inhalation of 5 breaths of diluent, delivered by a Bell and Gossett Compressor (Model LCHB, Morton Grove, Ill.) adjusted to a flow rate of 6 liters per minute using a Vaponefrin nebulizer (Fisons, New Bedford, Mass.), studies were repeated. This diluent value served as a control, and testing proceeded if $FEV_1$ was not reduced by 10% or more. Diluent was a sterile aqueous solution (pH = 7.0) of 0.036% potassium phosphate, 0.107% sodium phosphate, 0.40% phenol, and 0.50% sodium chloride obtained from Greer Laboratories, Lenoir, N.C. Pulmonary functions were performed with a Medistor spirometer (Simlog Instruments, Redmond, Washington) calibrated with a 1.5 liter syringe.

For the methacholine challenge, 5 breaths of serial dilutions of methacholine were given following the diluent measure. Spirometric measures were made 3 minutes thereafter. A positive test was a greater than 20% reduction in the 3-minute reading from the diluent value. If the test was negative, 5 breaths of the next dilution was given. Eight dilution increments were used: 0.15, 0.31, 0.62, 1.25, 2.5, 5.0, 10.0, and 25.0 mg/ml. The end point was that methacholine concentration producing at least a 20% decrease in $FEV_1$ from diluent control.

For histamine, 5 breaths of serial dilutions followed the diluent measure. Spirometry was performed 3 minutes thereafter. A positive test was a 3-minute decrease in $FEV_1$ of 20% or greater from the diluent value. If the test was negative, 5 breaths of the next dilution were given. Eight dilution increments were used: 0.06, 0.12, 0.25, 0.50, 1.0, 2.5, 5.0, and 10.0 mg/ml. The end point was that histamine concentration producing at least a 20% decrease in $FEV_1$ from diluent control.

Methacholine inhalation challenges were available for all patients during the summer period and 64 patients during the winter period. Using categories established previously, 32 patients were classified during summer as having low thresholds (0.15 and 0.31 mg/ml), 27 moderate thresholds (0.62, 1.25, and 2.5 mg/ml), and 17 as high thresholds (5.0, 10.0, and 25.0 mg/ml), with 4 patients having a negative methacholine challenge. During winter, 25 patients were classified as having low thresholds, 27 moderate, and 7 as high thresholds, with 5 patients having a negative methacholine challenge.

Histamine inhalation challenges were available for 66 patients during the summer period and 60 patients during the winter period. During the summer period, 18 patients had low thresholds (0.06 and 0.12 mg/ml), 27 had moderate thresholds (0.25, 0.50, and 1.0 mg/ml) and 17 had high thresholds (2.5, 5.0,

and 10.0 mg/ml), with 4 patients having a negative histamine challenge. During the winter period, 9 patients were classified as low, 30 as moderate, and 16 as high thresholds with 5 patients having a negative histamine challenge.

A final classification was based on the lowest threshold category of both methacholine and histamine inhalation challenges. For this classification, 66 patients had complete testing during the summer period and 58 patients during the winter period. During summer, 36 patients were classified within low, 23 within moderate, and 4 within high threshold categories, with 4 having negative challenges. During winter, 26 patients were classified within low, 24 within moderate, and 5 within high threshold categories, with 3 patients having negative challenges.

## 3.4 STATISTICAL ANALYSES

Separate analyses were performed for patients within both the summer and winter periods.

(A) Univariate regression and correlational analyses were performed for each individual within the summer and winter periods, relating each 24 hour air pollution and meterologic variable to the following 8:00 am pulmonary function measurements.

(B) The pattern of significant univariate regressions for individuals was then examined within groups defined by reaginic factors and airways hyperreactivity as indexed by methacholine and histamine challenges.

(C) Multivariate regression analyses using all 7 air pollution and meterologic variables and four concommittant variables (intraveneous bronchodilators given at the time of pulmonary function measurement, bronchodilators taken within 2 hours prior to pulmonary function measurement, bronchodilator treatments taken within one hour prior to pulmonary function measurement, and the previous day's 8:00 am pulmonary function) were performed next for all individuals within the summer and winter periods using leaps and bounds multiple linear regression procedures.[32] These analyses identified the best regression, defined as the regression providing the greatest gain in information (compared to no regression) indexed by the Akaike Information Coefficient (AIC).[33]

(D) The pattern of best multivariate regressions for individuals were then examined within groups defined by reaginic factors and airways hyperreactivity categories.

(E) Finally, multiple linear regression by leaps and bounds was then performed for all groups of patients defined by airways hyperreactivity and reaginic factors, using all 7 air pollution and meterologic variables and the 4 concommittant variables (see (3) above). For each group, the best regression was identified by the AIC criterion.

(F) The pattern of best regressions among groups defined by reaginic factors and airways hyperreactivity was examined to identify the role of air pollution and meterologic variables upon the pulmonary function measurements of subgroups of patients.

The final series of leaps and bounds multiple linear regression analyses, both for individuals (C and D) and groups (E and F), were performed for each of the 3 spirometric pulmonary function measures: (1) $FEV_1$, (2) $FEV_1/FVC\%$, and (3) PEFR.

## 4. RESULTS

### 4.1 AIR POLLUTION AND METEROLOGIC VARIABLES

Average monthly levels of each air pollution and meterologic variable studied are presented in Table 4.1 on the following page for the summer and winter periods. Each of the seasonal periods is subdivided into months in order to portray the consistency of the average levels during each period.

Table 4.2 shown on page 9 presents frequency distributions for each variable during the summer and winter periods, showing a marked increase in variability and the number of high levels for all air pollution variables during the winter period, with the exception of $O_3$. Minimum temperature and barometric pressure also showed more variability during winter. In comparison to the summer, mean daily levels for winter were higher for CO ($6.25 \pm 2.02$ vs $3.16 \pm 0.98$ ppm), THC ($2.95 \pm 0.55$ vs $2.33 \pm .24$ ppm), $SO_2$ ($0.006 \pm 0.004$ vs $0.003 \pm 0.003$ ppm), and COH ($0.59 \pm 0.22$ vs $0.25 \pm 0.07$), but winter values were clearly lower for $O_3$ than in the summer ($0.009 \pm 0.003$ vs $0.102 \pm 0.059$). $SO_2$ levels were generally low for both periods and showed little variability. Mean daily minimum temperature was $16C^{o}$ lower during winter ($-4.09C^{o}$) than summer ($11.95C^{o}$), with much greater variability represented in the winter values. Mean barometric pressure was slightly lower and varied more widely during winter ($627.3 \pm 4.3$) than summer ($629 \pm 2.9$).

Table 4.3 shown on page 10 presents the intercorrelations among all variables for each period. For both summer and winter periods, there were moderate to high correlations among $SO_2$, THC, and CO. For summer, $O_3$ was nearly independent of all other air pollution and meterologic variables, while in winter $O_3$ was inversely related to CO, $SO_2$, and THC. The index of particulates, COH, was positively related to CO, $SO_2$, and THC during the winter period, but inversely related to $O_3$. In contrast, during summer COH was essentially independent of $SO_2$ ($r = .05$) and $O_3$ ($r = .07$). Finally, as would be expected, minimum temperature was essentially unrelated to the air pollution variables during summer, but negatively related to COH during winter ($r = -.30$). Scatterplots did not indicate anything other than a linear trend in any of the data.

TABLE 4.1. MEANS AND STANDARD DEVIATIONS FOR ALL AIR POLLUTION AND METEROLOGIC VARIABLES BY MONTH FOR THE SUMMER (A) AND WINTER (B) PERIODS

| | | Carbon Monoxide (CO) ppm | | Sulphur Dioxide ($SO_2$) ppm | | Total Hydrocarbons (THC) ppm | | Ozone ($O_3$) ppm | | Coef. of Haze (COH) COHs/1000 ft | | Min Temp C° | | Barometric Pressure (BP) mmHg | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| A. Summer Period | N | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| May 1, 1975-May 31, 1975 | 31 | 2.960 | 1.107 | 0.003 | 0.005 | 2.265 | 0.284 | 0.107 | 0.057 | 0.230 | 0.073 | 6.403 | 3.562 | 627.46 | 4.164 |
| June 1, 1975-June 30, 1975 | 30 | 3.254 | 1.128 | 0.002 | 0.003 | 2.283 | 0.165 | 0.095 | 0.050 | 0.226 | 0.067 | 11.583 | 3.187 | 629.44 | 2.533 |
| July 1, 1975-July 31, 1975 | 31 | 3.095 | 0.580 | 0.003 | 0.002 | 2.352 | 0.198 | 0.100 | 0.068 | 0.270 | 0.062 | 14.226 | 1.564 | 632.05 | 2.040 |
| Aug. 1, 1975-Aug. 12, 1975 | 12 | 3.629 | 1.289 | 0.004 | 0.002 | 2.384 | 0.287 | 0.1f4 | 0.063 | 0.283 | 0.115 | 13.167 | 1.723 | 631.13 | 2.457 |
| B. Winter Period | | | | | | | | | | | | | | | |
| Nov. 15, 1975-Nov. 30, 1975 | 16 | 6.168 | 1.975 | 0.009 | 0.006 | 3.093 | 0.691 | 0.008 | 0.002 | 0.686 | 0.242 | -6.187 | 5.645 | 627.38 | 5.737 |
| Dec. 1, 1975-Dec. 31, 1975 * | 25 | 7.129 | 2.407 | 0.007 | 0.003 | 3.300 | 0.619 | 0.005 | 0.002 | 0.700 | 0.218 | -2.900 | 5.605 | 629.12 | 4.100 |
| Jan. 1, 1976-Jan. 31, 1976 | 30 | 7.247 | 2.592 | 0.008 | 0.007 | 3.200 | 1.187 | 0.006 | 0.003 | 0.719 | 0.298 | -6.900 | 6.073 | 629.12 | 4.124 |
| Feb. 1, 1976-Feb. 29, 1976 | 29 | 5.802 | 1.950 | 0.005 | 0.003 | 2.712 | 0.355 | 0.010 | 0.004 | 0.422 | 0.146 | -2.414 | 5.622 | 626.39 | 3.504 |
| Mar. 1, 1976-Mar. 31, 1976 | 31 | 5.032 | 1.262 | 0.004 | 0.003 | 2.582 | 0.365 | 0.014 | 0.005 | 0.487 | 0.185 | -2.806 | 5.927 | 624.90 | 4.712 |

* Six days at the end of December were excluded (December 25 through December 31).

TABLE 4.2. FREQUENCY DISTRIBUTIONS (DAYS) OF AIR POLLUTION AND METEROLOGIC VARIABLES FOR SUMMER AND WINTER PERIODS

| Carbon Monoxide (CO) | | | Sulfur Dioxide ($SO_2$) | | | Coefficient of Haze (COH) | | | Total Hydrocarbons (THC) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ppm | Summer | Winter | ppm | Summer | Winter | COHS/1000 ft | Summer | Winter | ppm | Summer | Winter |
| | | | | | | | | | 5.6 - 6.0 | 0 | 1 |
| | | | | | | 1.5 - 1.6 | 0 | 2 | 5.1 - 5.5 | 0 | 0 |
| | | | | | | 1.3 - 1.4 | 0 | 0 | 4.6 - 5.0 | 0 | 5 |
| 13.0 - 14.0 | 0 | 4 | .026 - .030 | 1 | 1 | 1.1 - 1.2 | 0 | 8 | 4.1 - 4.5 | 0 | 4 |
| 11.0 - 12.0 | 0 | 2 | .021 - .025 | 0 | 2 | .9 - 1.0 | 0 | 9 | 3.6 - 4.0 | 0 | 9 |
| 9.0 - 10.0 | 0 | 26 | .016 - .020 | 0 | 5 | .7 - .8 | 0 | 27 | 3.1 - 3.5 | 1 | 25 |
| 7.0 - 8.0 | 2 | 43 | .011 - .015 | 0 | 13 | .5 - .6 | 0 | 42 | 2.6 - 3.0 | 9 | 43 |
| 5.0 - 6.0 | 12 | 35 | .006 - .010 | 9 | 39 | .3 - .4 | 50 | 42 | 2.1 - 2.5 | 88 | 43 |
| 3.0 - 4.0 | 77 | 20 | .001 - .005 | 82 | 67 | .1 - .2 | 51 | 1 | 1.6 - 2.0 | 3 | 1 |
| 0.0 - 2.0 | 10 | 1 | Zero | 9 | 4 | | | | | | |
| No. of days | 101 | 131 | No. of days | 101 | 131 | No. of days | 101 | 131 | No. of days | 101 | 131 |
| $\bar{X} \pm SD$ | 3.16±.98 | 6.25±2.02 | $\bar{X} \pm SD$ | .003±.003 | .006±.004 | $\bar{X} \pm SD$ | .25±.07 | .59±.22 | $\bar{X} \pm SD$ | 2.33±.24 | 2.95±.55 |

| Ozone ($O_3$) | | | Minimum Temperature (T) | | | Barometric Pressure (BP) | | |
|---|---|---|---|---|---|---|---|---|
| ppm | Summer | Winter | C° | Summer | Winter | mmHg | Summer | Winter |
| | | | +16 - +20 | 32 | 0 | | | |
| .23 - .26 | 2 | 0 | +11 - +15 | 34 | 1 | | | |
| .19 - .22 | 7 | 0 | + 6 - +10 | 19 | 4 | | | |
| .15 - .18 | 20 | 0 | + 1 - + 5 | 15 | 33 | 633 - 636 | 16 | 14 |
| .11 - .14 | 15 | 0 | - 4 - 0 | 1 | 44 | 629 - 632 | 59 | 44 |
| .07 - .10 | 26 | 0 | - 9 - - 5 | 0 | 19 | 625 - 628 | 21 | 43 |
| .03 - .06 | 18 | 3 | -14 - -10 | 0 | 23 | 621 - 624 | 2 | 20 |
| .00 - .02 | 13 | 128 | -19 - -15 | 0 | 7 | 617 - 620 | 3 | 10 |
| No. of days | 101 | 131 | No. of days | 101 | 131 | No. of days | 101 | 131 |
| $\bar{X} \pm SD$ | .102±.060 | .009±.003 | $\bar{X} \pm SD$ | +11.95±2.65 | -4.09±5.80 | $\bar{X} \pm SD$ | 629.8±2.9 | 627.3±4.3 |

TABLE 4.3. INTERCORRELATIONS AMONG AIR POLLUTION AND METEROLOGIC VARIABLES FOR THE SUMMER (A) AND WINTER (B) PERIODS

A. Summer Period

| | CO | $SO_2$ | THC | $O_3$ | COH | Avtemp | Mintemp |
|---|---|---|---|---|---|---|---|
| $SO_2$ | .42** | | | | | | |
| THC | .69** | .42** | | | | | |
| $O_3$ | .00 | .20* | -.04 | | | | |
| COH | .50** | .05 | .62** | .07 | | | |
| Avtemp | .10 | .10 | .08 | -.01 | .16 | | |
| Mintemp | .10 | .07 | .10 | -.01 | .18 | .95** | |
| Barometric Pressure | -.04 | -.16 | .16 | -.16 | .18 | .29** | .31** |

B. Winter Period

| | CO | $SO_2$ | THC | $O_3$ | COH | Avtemp | Mintemp |
|---|---|---|---|---|---|---|---|
| $SO_2$ | .44** | | | | | | |
| THC | .71** | .56** | | | | | |
| $O_3$ | -.58** | -.34** | -.49** | | | | |
| COH | .76** | .64** | .73** | -.54** | | | |
| Avtemp | .21* | -.17 | -.09 | .11 | -.30** | | |
| Mintemp | .20* | -.18 | -.11 | .12 | -.30** | .95** | |
| Barometric Pressure | .08 | -.03 | .12 | -.24* | .08 | -.20* | -.18 |

*P<.05.

**P<.01.

## 4.2 PULMONARY FUNCTION MEASUREMENTS

Table 4.4 below presents the distributions of the mean pulmonary functions for both periods. For the separate groups of 67 patients within both periods, the pulmonary functions were distributed in a similar way: $FEV_1$ (2.04 ± .57 vs 2.08 ± .72 liters, for summer and winter, respectively), PEFR (6.22 ± 1.69 vs 6.17 ± 1.97 liters/sec), and $FEV_1/FVC\%$ (73.97 ± 9.54 vs 72.25 ± 9.97 per cent).

TABLE 4.4. FREQUENCY DISTRIBUTIONS OF MEAN PULMONARY FUNCTION MEASURES FOR PATIENTS DURING SUMMER AND WINTER PERIODS

| First Second Forced Expiratory Volume ($FEV_1$) | | | $FEV_1$ as a Percent of Forced Vital Capacity ($FEV_1/FVC\%$) | | |
|---|---|---|---|---|---|
| Liters | Summer | Winter | Percent | Summer | Winter |
| | | | 96 - 100 | 1 | 0 |
| | | | 91 - 95 | 2 | 1 |
| 4.51 - 5.00 | 0 | 1 | 86 - 90 | 3 | 7 |
| 4.01 - 4.50 | 0 | 0 | 81 - 85 | 10 | 6 |
| 3.51 - 4.00 | 0 | 2 | 76 - 80 | 16 | 9 |
| 3.01 - 3.50 | 2 | 2 | 71 - 75 | 11 | 18 |
| 2.51 - 3.00 | 13 | 9 | 66 - 70 | 10 | 10 |
| 2.01 - 2.50 | 19 | 21 | 61 - 65 | 8 | 5 |
| 1.51 - 2.00 | 22 | 19 | 56 - 60 | 5 | 9 |
| 1.01 - 1.50 | 9 | 10 | 51 - 55 | 1 | 1 |
| .51 - 1.00 | 2 | 3 | 46 - 50 | 0 | 1 |
| N/Period | 67 | 67 | N/Period | 67 | 67 |
| $\bar{X}$ ± SD | 2.04±.57 | 2.08±.72 | $\bar{X}$ ± SD | 74.0±9.5 | 72.2±10.0 |

| Peak Expiratory Flow Rate (PEFR) | | |
|---|---|---|
| Liters/Sec | Summer | Winter |
| 12.01 - 13.00 | 0 | 1 |
| 11.01 - 12.00 | 1 | 0 |
| 10.01 - 11.00 | 0 | 3 |
| 9.01 - 10.00 | 1 | 3 |
| 8.01 - 9.00 | 5 | 3 |
| 7.01 - 8.00 | 16 | 5 |
| 6.01 - 7.00 | 15 | 18 |
| 5.01 - 6.00 | 13 | 17 |
| 4.01 - 5.00 | 10 | 10 |
| 3.01 - 4.00 | 5 | 6 |
| 2.01 - 3.00 | 0 | 0 |
| 1.01 - 2.00 | 1 | 1 |
| N/Period | 67 | 67 |
| $\bar{X}$ ± SD | 6.22±1.69 | 6.17±1.97 |

To evaluate the relationships among the three pulmonary function measures, correlations were performed for each patient using all available days within the respective periods. The average correlations, and standard deviations, are presented in Table 4.5 for the summer and winter periods. For patients

TABLE 4.5. MEANS AND STANDARD DEVIATIONS OF THE CORRELATION COEFFICIENTS AMONG PULMONARY FUNCTION MEASUREMENTS FOR THE SUMMER AND WINTER PERIODS*

| Period | Pulmonary Function | $FEV_1$ | $FEV_1$/FVC% | PEFR |
|---|---|---|---|---|
| Summer | $FEV_1$ | ---- | .54±.32 | .84±.15 |
| | $FEV_1$/FVC% | | ---- | .48±.31 |
| | PEFR | | | ---- |
| Winter | $FEV_1$ | ---- | .59±.36 | .78±.25 |
| | $FEV_1$/FVC% | | ---- | .50±.33 |
| | PEFR | | | ---- |

* Data are expressed as Mean ± SD.

within both periods, the pattern of the mean correlations is similar: $FEV_1$ and PEFR are highly related, while the relationships among $FEV_1$/FVC% and the other measures are only moderate. Since the pulmonary function measurements were not uniformly highly related and since no single pulmonary function was clearly preferable, analyses relating pulmonary functions to air pollution and meterologic variables were subsequently performed using each measure.

It had been anticipated that patients would show generally improving pulmonary function levels throughout hospitalization. Preliminary correlational analyses, relating pulmonary functions to day of study were performed

to evaluate this expected trend. Table 4.6 summarizes the distribution of these correlations for each pulmonary function measure for patients within both summer and winter periods. Correlations within both periods varied widely and

TABLE 4.6. FREQUENCY DISTRIBUTIONS OF CORRELATIONS BETWEEN PULMONARY FUNCTION MEASURES AND DAY OF STUDY FOR SUMMER AND WINTER PERIODS

| | Pulmonary Function Measurements* | | | | | |
|---|---|---|---|---|---|---|
| | $FEV_1$ | | $FEV_1/FVC\%$ | | PEFR | |
| Correlation | Summer | Winter | Summer | Winter | Summer | Winter |
| .81 to 1.00 | 0 | 4 | 0 | 1 | 1 | 1 |
| .61 to .80 | 9 | 4 | 8 | 3 | 9 | 12 |
| .41 to .60 | 9 | 14 | 13 | 16 | 13 | 12 |
| .21 to .40 | 13 | 7 | 14 | 10 | 15 | 5 |
| .01 to .20 | 17 | 7 | 9 | 6 | 14 | 7 |
| -.19 to .00 | 10 | 6 | 7 | 8 | 10 | 13 |
| -.39 to -.20 | 7 | 8 | 9 | 7 | 3 | 5 |
| -.59 to -.40 | 2 | 10 | 6 | 9 | 1 | 7 |
| -.79 to -.60 | 0 | 6 | 1 | 7 | 1 | 3 |
| -.99 to -.80 | 0 | 1 | 0 | 0 | 0 | 1 |
| N/Period | 67 | 67 | 67 | 67 | 67 | 67 |
| $\bar{X} \pm SD$ | .19±.32 | .05±.50 | .16±.39 | .04±.45 | .25±.36 | .13±.46 |

* $FEV_1$ = First Second Forced Expiratory Volume; $FEV_1/FVC\%$ = $FEV_1$ as a % of Forced Vital Capacity; PEFR = Peak Expiratory Flow Rate.

were not consistently positive. For example, for PEFR, 15 correlations were in the range of 0 to -.60 for the summer period, while 29 were within this range for the winter period. These analyses confirmed visual examination of individual plots of pulmonary functions made across days of treatment, and indicated that a wide range of patterns - random, increasing, decreasing, etc. existed. Specific patterns could not be attributable to patients within groups defined by airways hyperreactivity or reaginic factors.

## 4.3 PULMONARY FUNCTIONS IN RELATION TO AIR POLLUTION AND METEROLOGIC FACTORS

### 4.3.1 Univariate Regression Analyses

Simple regressions were performed to provide an initial impression of the relationship between pulmonary function measures ($FEV_1/FVC\%$) and the air pollution/meterologic variables. All analyses were performed on individual patients, thereby providing a matrix of regression equations for the summer and winter periods defined by 67 patients per period and 7 air pollution and meterologic variables. Scatterplots indicated no trends beyond the linear in the data.

Table 4.7 summarizes the significant regressions for each variable. Air pollution variables failed to show a consistent relationship to $FEV_1/FVC\%$

TABLE 4.7. UNIVARIATE REGRESSION ANALYSES SUMMARY TABLE FOR INDIVIDUAL REGRESSIONS

| Period | Regression Coefficient | Air Pollution - Meterologic Variable | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | CO | $SO_2$ | THC | $O_3$ | COH | T* | BP |
| Summer | Positive | 1 | 5 | 3 | 1 | 4 | 6 | 13 |
| | Negative | 2 | 3 | 1 | 3 | 1 | 3 | 2 |
| | Not Significant † | 64 | 59 | 63 | 63 | 62 | 58 | 52 |
| | N/Period = 67 | | | | | | | |
| Winter | Positive | 5 | 2 | 3 | 5 | 8 | 5 | 2 |
| | Negative | 1 | 2 | 4 | 11 | 6 | 7 | 3 |
| | Not Significant † | 61 | 63 | 60 | 51 | 53 | 55 | 62 |
| | N/Period = 67 | | | | | | | |

* Minimum Temperature.

† $P<.05$.

measurements. For example, during the winter period COH was significantly related to $FEV_1$/FVC% for 14 patients; but of these, 8 regression coefficients were positive (higher values of COH associated with higher values of $FEV_1$/FVC%) while only 6 were in the expected negative direction. Surprisingly, ozone ($O_3$) was significant for 14 individuals during winter; however, 5 of these 14 individuals had higher $FEV_1$/FVC% associated with higher levels of $O_3$. There were no differences in age, sex, airways hyperreactivity or reaginic factors among patients with positive, negative, or nonsignificant regressions for any air pollution variable.

Barometric pressure was significantly associated with $FEV_1$/FVC% during the summer period for 15 patients, with 13 of these patients having higher $FEV_1$/FVC% on days of higher barometric pressure. No consistent differences could be found between patients apparently affected by barometric pressure and others. During the winter period, barometric pressure exerted virtually no consistent effect upon $FEV_1$/FVC%. Minimum temperature was unrelated to $FEV_1$/FVC% either during the summer or winter periods.

### 4.3.2 Multivariate Regression Analyses

In these final series of analyses, extensive efforts were made to account for variables which could obscure a real relationship between air pollution/meterologic variables and pulmonary function measures.

A total of eleven variables were involved in leaps and bounds multiple linear regression analyses,[32] using all 7 air pollution/meterologic variables and 4 concomittant variables shown in Table 4.8. The concomittant variables included (1) intraveneous bronchodilators given at the time of the pulmonary function measurement, (2) the previous day's pulmonary function value, (3) bronchodilator medications taken within 2 hours prior to pulmonary function measurement, and (4) bronchodilator treatments taken within 1 hour prior to pulmonary function measurement. The previous day's pulmonary function measurement was included to account for the usual variations noted across time in the level of airway obstruction, while each of the remaining 3 variables could influence airway calibre directly.

As described in the Methods section, identical analyses were performed for $FEV_1$, $FEV_1$/FVC%, and for PEFR for (A) individual patients within each period, (B) patient groups defined by the role of reaginic factors in their asthma, and (C) patient groups defined by airways hyperreactivity, indexed by methacholine and histamine challenges.

A summary table for the leaps and bounds multiple linear regression analyses for individual patients is presented in Table 4.9. The table shows the frequency with which each variable appeared within the best regression equation selected according to the AIC criterion.[33] As expected, prior bronchodilator treatments clearly influenced subsequent pulmonary function measures, appearing most often within the best regression for all pulmonary function measures for both periods. With few exceptions, prior bronchodilator treatment was positively related to pulmonary function levels. The next strongest variable was the presence of

TABLE 4.8. VARIABLES INCLUDED IN THE LEAPS AND BOUNDS MULTIPLE LINEAR REGRESSION ANALYSES

| Variable No. | Name | Value | Description |
|---|---|---|---|
| 1 | Intraveneous bronchodilators | 1,0 | Intraveneous bronchodilators given at time of pulmonary function measurement |
| 2 | Previous day's function | Raw value | 8:00 am pulmonary function for the preceding day |
| 3 | Prior bronchodilators | 1,0 | Bronchodilators taken within two hours preceding pulmonary function measurement |
| 4 | Prior treatment | 1,0 | Inhaled bronchodilator treatment taken within 1 hour preceding pulmonary function measurement |
| 5 | Carbon monoxide (CO) | ppm | 24-hour average preceding 8:00 am pulmonary function |
| 6 | Sulfur dioxide ($SO_2$) | ppm | " |
| 7 | Total hydrocarbons (THC) | ppm | " |
| 8 | Ozone ($O_3$) | ppm | " |
| 9 | Coefficient of haze (COH) | COHs/1000 ft | " |
| 10 | Minimum temperature (T) | $C^o$ | " |
| 11 | Barometric pressure (BP) | mmHg | " |

TABLE 4.9. SUMMARY TABLE FOR LEAPS AND BOUNDS MULTIPLE LINEAR REGRESSION ANALYSES FOR INDIVIDUAL PATIENTS

| Variable | | Summer Period | | | | | | | | | Winter Period | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $FEV_1$ | | | $FEV_1/FVC\%$ | | | PEFR | | | $FEV_1$ | | | $FEV_1/FVC\%$ | | | PEFR | | |
| Number | Variable Name | + | - | No* | + | - | No | + | - | No | + | - | No | + | - | No | + | - | No |
| 1 | Intraveneous Bronchodilators | 3 | 15 | 49 | 7 | 10 | 50 | 3 | 16 | 48 | 3 | 17 | 47 | 6 | 11 | 50 | 4 | 13 | 50 |
| 2 | Previous Function | 1 | 9 | 57 | 4 | 5 | 58 | 0 | 8 | 59 | 1 | 6 | 60 | 3 | 6 | 58 | 2 | 7 | 58 |
| 3 | Prior Bronchodilators | 3 | 15 | 49 | 2 | 10 | 55 | 6 | 14 | 47 | 1 | 12 | 54 | 8 | 6 | 53 | 2 | 9 | 56 |
| 4 | Prior Treatments | 29 | 3 | 35 | 16 | 5 | 46 | 31 | 4 | 32 | 27 | 4 | 36 | 21 | 9 | 37 | 28 | 6 | 33 |
| 5 | CO | 3 | 5 | 59 | 6 | 7 | 54 | 5 | 4 | 58 | 3 | 5 | 59 | 6 | 3 | 58 | 5 | 5 | 57 |
| 6 | $SO_2$ | 4 | 3 | 60 | 3 | 5 | 59 | 4 | 4 | 59 | 4 | 9 | 54 | 2 | 6 | 59 | 3 | 7 | 57 |
| 7 | THC | 3 | 1 | 63 | 4 | 3 | 60 | 3 | 3 | 61 | 2 | 6 | 59 | 2 | 4 | 61 | 5 | 6 | 56 |
| 8 | $O_3$ | 11 | 2 | 54 | 2 | 6 | 59 | 7 | 2 | 58 | 5 | 9 | 53 | 1 | 6 | 60 | 9 | 8 | 50 |
| 9 | COH | 7 | 3 | 57 | 7 | 3 | 57 | 5 | 1 | 61 | 11 | 4 | 52 | 7 | 6 | 54 | 10 | 5 | 52 |
| 10 | Temperature | 14 | 3 | 50 | 14 | 2 | 51 | 13 | 1 | 53 | 8 | 4 | 55 | 2 | 8 | 57 | 5 | 7 | 55 |
| 11 | Barometric Pressure | 8 | 0 | 59 | 7 | 3 | 57 | 7 | 0 | 60 | 2 | 2 | 63 | 5 | 3 | 59 | 4 | 2 | 61 |

* Header labels indicate: + = positive regression coefficient ($P<.05$); - = negative regression coefficient ($P<.05$); No = not significant.

intraveneous bronchodilators at the time of pulmonary function measurement; it was generally associated with lower pulmonary functions since patients are typically placed on these intensive regimens when experiencing major breathing difficulties.

More importantly, the difficulty in constructing a general model is apparent. No consistent relationship between any air pollution/meterologic variables and any of the pulmonary function measures were found. When air pollution variables appeared within the best regression, they were nearly evenly distributed between positive and negative regression coefficients. For the meterologic variables, minimum temperature appeared with a positive regression coefficient 14 times during the summer period for each pulmonary function measure, and with a negative coefficient rarely. Unexpectedly, temperature was less consistently related to pulmonary function during the winter period, suggesting that limited exposure may occur to the outdoors on cold winter days. Barometric pressure was generally positive when it appeared during summer, but not consistently related to pulmonary functions for the winter period.

Finally, Table 4.9 indicates that there were patients within both seasonal periods where no best regression could be identified on the basis of the AIC criterion.

Supplementary analyses indicated that the presence or absence of reaginic factors in asthma, and degree of airways hyperreactivity (indexed by methacholine and histamine challenges) could not differentiate between patients having or not having significant negative regression coefficients for air pollution or temperature within the best regressions.

Tables 4.10 and 4.11, shown on the following pages, summarize the final leaps and bounds multiple linear regression analyses for the summer and winter periods, performed for groups of patients defined according to airways hyperreactivity. Analyses for groups defined according to reaginic factors revealed no systematic differences among these groups, and reaginic factors were therefore disregarded as a basis for subsequent grouping.

In agreement with the parallel analyses for individuals, prior bronchodilator treatments taken within one hour before pulmonary function measurement (Var. #4) appeared most often within the best regression of these groups, and invariably with a positive regression coefficient. Intraveneous bronchodilators (Var. #1), in contrast, invariably had a negative regression coefficient within the best regressions, indicating that patients are generally experiencing breathing difficulty when placed on these regimens.

The 5 air pollution variables appeared rarely within the best regression for these groups, and typically later than the medication variables. While the pattern of results is generally similar for all pulmonary function measures, careful examination of the table reveals inconsistencies in the direction of the relationships. For example, when $O_3$ (Var. #8) appeared, it was generally negatively related in winter. The only time it appeared in summer (for $FEV_1$), $O_3$ was positively related to the pulmonary function measurement. For CO

TABLE 4.10. LEAPS AND BOUNDS MULTIPLE LINEAR REGRESSION ANALYSES SUMMARY TABLE FOR SUMMER PERIOD SUMMARIZING BEST REGRESSIONS FOR AIRWAYS HYPERREACTIVITY GROUPS*

| Group | N | Coefficient of Determination $R^2$ | Variable A | | | Variable B | | | Variable C | | | Variable D | | | Variable E & (F) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P |
| A. $FEV_1$ | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 0 | ---- | ---- | ---- | ---- | ---- | ---- | ---- | | | | | | | | | |
| Low | 32 | 4.365 | 1 | - | <.001 | 2 | + | <.05 | 4 | + | <.05 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 27 | 5.379 | 1 | - | <.01 | 4 | + | <.001 | 9 | + | <.05 | | | | | | |
| High | 5 | 2.362 | 1 | - | <.10 | 4 | + | <.001 | | | | | | | | | |
| Negative | 3 | 6.419 | 4 | - | <.05 | 8 | + | <.01 | 9 | + | <.01 | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | |
| Missing | 1 | 25.65 | 4 | + | <.001 | 10 | + | <.05 | | | | | | | | | |
| Low | 18 | 3.749 | 1 | - | <.01 | 4 | + | <.001 | 8 | + | <.05 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 27 | 3.917 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | | | | | | |
| High | 17 | 4.492 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | | | | | | |
| Negative | 4 | ---------- No regression is best ---------- | | | | | | | | | | | | | | | |
| Lowest | | | | | | | | | | | | | | | | | |
| Missing | 1 | 25.65 | 4 | + | <.001 | 10 | + | <.05 | | | | | | | | | |
| Low | 36 | 3.727 | 1 | - | <.001 | 2 | + | <.05 | 4 | + | <.001 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 23 | 6.237 | 1 | - | <.001 | 4 | + | <.001 | 9 | + | <.05 | 10 | + | <.05 | | | |
| High | 4 | 1.917 | 1 | - | <.10 | 4 | + | <.01 | | | | | | | | | |
| Negative | 3 | 6.419 | 4 | - | <.05 | 8 | + | <.01 | 9 | + | <.01 | | | | | | |

TABLE 4.10. continued

| Group | N | Coefficient of Determination $R^2$ | Variable A | | | Variable B | | | Variable C | | | Variable D | | | Variable E & (F) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Regression Var. | Coef. | P | Regression Var. | Coef. | P | Regression Var. | Coef. | P | Regression Var. | Coef. | P | Regression Var. | Coef. | P |
| B. $FEV_1/FVC\%$ | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 0 | ---- | ---- | ---- | ---- | ---- | ---- | ---- | | | | | | | | | |
| Low | 32 | 2.524 | 3 | - | <.01 | 4 | + | <.001 | 5 | - | <.01 | 6 | + | <.10 | 10&(11) | +(+) | <.001 |
| Moderate | 27 | 1.239 | 1 | - | <.01 | 4 | + | <.001 | 10 | + | <.05 | 11 | + | <.10 | | | &(<.05) |
| High | 5 | 2.309 | 1 | - | <.10 | 4 | + | <.01 | 10 | + | <.05 | | | | | | |
| Negative | 3 | 1.725 | 5 | - | <.10 | 9 | + | <.05 | | | | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | |
| Missing | 1 | 19.36 | 4 | + | <.01 | 10 | + | <.01 | | | | | | | | | |
| Low | 18 | 3.435 | 1 | - | <.10 | 4 | + | <.001 | 6 | - | <.10 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 27 | .589 | 1 | - | <.05 | 4 | + | <.01 | 10 | + | <.05 | | | | | | |
| High | 17 | 3.031 | 1 | - | <.001 | 2 | + | <.10 | 4 | + | <.001 | 5 | - | <.04 | 10 | + | <.001 |
| Negative | 4 | 2.252 | 4 | + | <.01 | | | | | | | | | | | | |
| Lowest † | | | | | | | | | | | | | | | | | |
| Missing | 1 | 19.36 | 4 | + | <.01 | 10 | + | <.01 | | | | | | | | | |
| Low | 36 | 2.716 | 1 | - | <.001 | 2 | + | <.05 | 4 | + | <.001 | 5 | - | <.01 | 10 | + | <.001 |
| Moderate | 23 | 0.702 | 1 | - | <.05 | 4 | + | <.001 | 9 | + | <.10 | 11 | + | <.01 | | | |
| High | 4 | 2.275 | 1 | - | <.20 | 4 | + | <.05 | 10 | + | <.05 | | | | | | |
| Negative | 3 | 1.725 | 5 | - | <.10 | 9 | + | <.05 | | | | | | | | | |

TABLE 4.10. continued

| Group | N | Coefficient of Determination $R^2$ | Variable A Var. | Variable A Regression Coef. | Variable A P | Variable B Var. | Variable B Regression Coef. | Variable B P | Variable C Var. | Variable C Regression Coef. | Variable C P | Variable D Var. | Variable D Regression Coef. | Variable D P | Variable E & (F) Var. | Variable E & (F) Regression Coef. | Variable E & (F) P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C. PEFR | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 0 | ---- | ---- | ---- | ---- | ---- | ---- | ---- | | | | | | | | | |
| Low | 32 | 4.998 | 1 | - | <.001 | 2 | + | <.05 | 4 | + | <.001 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 27 | 6.086 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | | | | | | |
| High | 5 | 1.383 | 4 | + | <.01 | | | | | | | | | | | | |
| Negative | 3 | ---------- No regression is best ---------- | | | | | | | | | | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | |
| Missing | 1 | 45.24 | 1 | - | <.01 | 4 | + | <.001 | 10 | + | <.05 | | | | | | |
| Low | 18 | 4.498 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | 11 | + | <.05 | | | |
| Moderate | 27 | 4.863 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | | | | | | |
| High | 17 | 3.786 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.01 | 11 | + | <.10 | | | |
| Negative | 4 | 2.918 | 4 | + | <.001 | | | | | | | | | | | | |
| Lowest | | | | | | | | | | | | | | | | | |
| Missing † | 1 | 45.24 | 1 | - | <.01 | 4 | + | <.001 | 10 | + | <.05 | | | | | | |
| Low | 36 | 4.311 | 1 | - | <.001 | 2 | + | <.05 | 4 | + | <.001 | 10 | + | <.001 | 11 | + | <.01 |
| Moderate | 23 | 6.688 | 1 | - | <.001 | 4 | + | <.001 | 10 | + | <.001 | | | | | | |
| High | 4 | 0.928 | 4 | + | <.10 | | | | | | | | | | | | |
| Negative | 3 | 2.596 | 3 | - | <.10 | 7 | + | <.10 | 10 | - | <.10 | | | | | | |

• Variable Code: 1 = Intraveneous bronchodilators; 2 = previous day's pulmonary function; 3 = prior bronchodilators; 4 = prior treatments; 5 = CO; 6 = $SO_2$; 7 = THC; 8 = $O_3$; 9 = COH; 10 = minimum temperature; 11 = barometric pressure.

† Note - This is the same group as missing histamine above.

TABLE 4.11. LEAPS AND BOUNDS MULTIPLE LINEAR REGRESSION ANALYSES SUMMARY TABLE FOR WINTER PERIOD SHOWING BEST REGRESSIONS FOR AIRWAYS HYPERREACTIVITY GROUPS *

| Group | N | Coefficient of Determination $R^2$ | Variable A | | | Variable B | | | Variable C | | | Variable D | | | Variable E & (F) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P | Var. | Regression Coef. | P |
| A. $FEV_1$ | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 3 | 2.323 | 4 | + | <.10 | 8 | - | <.05 | | | | | | | | | |
| Low | 25 | 1.417 | 1 | - | <,001 | 2 | - | <.10 | 4 | + | <.001 | 5 | - | <.05 | 9 | + | <.01 |
| Moderate | 27 | 2.706 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| High | 7 | 8.319 | 1 | - | <.001 | 4 | + | <.001 | 8 | - | <.05 | | | | | | |
| Negative | 5 | 20.973 | 3 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | <.001 |
| Missing | 7 | 8.880 | 1 | - | <.05 | 2 | - | <.01 | 4 | + | <.001 | 5 | - | <.10 | 9&(10) | +(+) | &(<.01) |
| Low | 9 | 2.202 | 1 | - | <.01 | 4 | + | <.001 | 6 | - | <.05 | 8 | + | <.10 | 9 | + | <.05 |
| Moderate | 30 | 0.882 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| High | 16 | 5.593 | 1 | - | <.001 | 4 | + | <.001 | 11 | + | <.05 | | | | | | |
| Negative | 5 | 9.424 | 1 | - | <.001 | 4 | + | <.001 | 8 | - | <.05 | | | | | | |
| Lowest | | | | | | | | | | | | | | | | | |
| Missing | 9 | 5.673 | 1 | - | <.01 | 4 | + | <.001 | 9 | + | <.01 | | | | | | |
| Low | 26 | .554 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| Moderate | 24 | 3.129 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| High | 5 | 9.379 | 1 | - | <.001 | 4 | + | <.001 | 8 | - | <.05 | | | | | | |
| Negative | 3 | 22.420 | 3 | - | <.001 | 4 | + | <.001 | | | | | | | | | |

TABLE 4.11. continued

| Group | N | Coefficient of Determination $R^2$ | Variable A Var. | Regression Coef. | P | Variable B Var. | Regression Coef. | P | Variable C Var. | Regression Coef. | P | Variable D Var. | Regression Coef. | P | Variable E & (F) Var. | Regression Coef. | P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| B. $FEV_1/FVC\%$ | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 3 | 0.885 | 10 | - | <.10 | | | | | | | | | | | | |
| Low | 25 | 0.764 | 1 | - | <.001 | 4 | + | <.001 | 10 | - | <.05 | | | | | | |
| Moderate | 27 | 0.980 | 3 | - | <.001 | 4 | + | <.001 | 8 | - | <.05 | | | | | | |
| High | 7 | 0.479 | 11 | + | <.05 | | | | | | | | | | | | |
| Negative | 5 | 7.800 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | |
| Missing | 7 | 0.525 | 8 | - | <.05 | | | | | | | | | | | | |
| Low | 9 | ---------- | | | | | | No regression is best | | | | | | | | | |
| Moderate | 30 | 0.855 | 1 | - | <.001 | 4 | + | <.001 | 5 | - | <.05 | 8 | - | <.05 | 9&(11) | +(-) | <.25 |
| High | 16 | 2.323 | 1 | - | <.001 | 4 | + | <.001 | 11 | + | <.01 | | | | | | &(<.01) |
| Negative | 5 | ---------- | | | | | | No regression is best | | | | | | | | | |
| Lowest | | | | | | | | | | | | | | | | | |
| Missing | 9 | 0.736 | 8 | - | <.01 | | | | | | | | | | | | |
| Low | 26 | 0.736 | 1 | - | <.001 | 4 | + | <.001 | 10 | - | <.01 | | | | | | |
| Moderate | 24 | 1.059 | 3 | - | <.001 | 4 | + | <.001 | 8 | - | <.10 | | | | | | |
| High | 5 | 0.933 | 1 | - | <.10 | 4 | + | <.05 | | | | | | | | | |
| Negative | 3 | 9.847 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |

TABLE 4.11. continued

| Group | N | Coefficient of Determination $R^2$ | Variable A Var. | Variable A Regression Coef. | Variable A P | Variable B Var. | Variable B Regression Coef. | Variable B P | Variable C Var. | Variable C Regression Coef. | Variable C P | Variable D Var. | Variable D Regression Coef. | Variable D P | Variable E & (F) Var. | Variable E & (F) Regression Coef. | Variable E & (F) P |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C. PEFR | | | | | | | | | | | | | | | | | |
| Methacholine | | | | | | | | | | | | | | | | | |
| Missing | 3 | 4.748 | 1 | - | <.05 | 4 | + | <.01 | 8 | - | <.05 | | | | | | |
| Low | 25 | 1.198 | 1 | - | <.001 | 4 | + | <.001 | 7 | - | <.05 | 8 | + | <.05 | 9 | + | <.001 |
| Moderate | 27 | 1.858 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| High | 7 | 6.038 | 1 | - | <.001 | 4 | + | <.001 | 8 | + | <.01 | 9 | + | <.05 | | | |
| Negative | 5 | 10.515 | 1 | - | <.01 | 4 | + | <.001 | | | | | | | | | |
| Histamine | | | | | | | | | | | | | | | | | |
| Missing | 7 | 8.199 | 2 | - | <.001 | 4 | + | <.001 | 9 | + | <.001 | | | | | | |
| Low | 9 | 1.725 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| Moderate | 30 | 0.479 | 1 | - | <.05 | 2 | - | <.10 | 4 | + | <.001 | | | | | | |
| High | 16 | 4.512 | 1 | - | <.001 | 4 | + | <.001 | 11 | + | <.01 | | | | | | |
| Negative | 5 | 7.629 | 3 | - | <.001 | 4 | + | <.001 | 6 | - | <.05 | 8 | - | <.001 | | | |
| Lowest | | | | | | | | | | | | | | | | | |
| Missing | 9 | 7.515 | 2 | - | <.001 | 4 | + | <.001 | 8 | - | <.05 | 9 | + | <.01 | | | |
| Low | 26 | 0.329 | 1 | - | <.05 | 4 | + | <.01 | 8 | + | <.10 | | | | | | |
| Moderate | 24 | 2.138 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| High | 5 | 7.449 | 1 | - | <.001 | 4 | + | <.001 | | | | | | | | | |
| Negative | 3 | 15.481 | 1 | - | <.001 | 4 | + | <.001 | 8 | + | <.05 | 9 | + | <.05 | | | |

• Variable Code: 1 = intraveneous bronchodilators; 2 = previous day's pulmonary function; 3 = prior bronchodilators; 4 = prior treatments; 5 = CO; 6 = $SO_2$; 7 = THC; 8 = $O_3$; 9 = COH; 10 = minimum temperature; 11 = barometric pressure.

(Var. #5), the pattern was somewhat more consistent, appearing twice as a negatively related variable in winter (for $FEV_1/FVC\%$ and $FEV_1$) and several times during summer (for $FEV_1/FVC\%$). $SO_2$ (Var. #6) appeared twice (for $FEV_1$ and PEFR) with a negative regression coefficient in winter and twice in summer (on $FEV_1/FVC\%$), but with a positive and a negative regression coefficient. THC (Var. #7) appeared only once in winter and with a negative regression coefficient (PEFR), and not at all for summer. Finally, COH (Var. #9) which appeared several times during summer ($FEV_1$ and PEFR) and winter ($FEV_1/FVC\%$ and $FEV_1$), always had a positive regression coefficient.

Patient groups defined according to airways hyperreactivity were not consistently influenced by air pollution variables in the same way. The regression equations could only account for a relatively small amount of the variability in the pulmonary function scores.

For the meterologic variables, minimum temperature (Var. #10) and barometric pressure (Var. #11), the results are also equivocal. Temperature and barometric pressure appeared rarely during the winter period, and with negative and positive regression coefficients. In contrast, during the summer period, minimum temperature appeared frequently and always with positive regression coefficiants, but this effect was not attributable to any group or groups defined by airways hyperreactivity. In summary, the specific influence of air pollution variables when they appeared, was small, variable in direction, inconsistent for groups defined by airways hyperreactivity, and inconsistent across pulmonary function measures ($FEV_1/FVC\%$, $FEV_1$, and PEFR).

## 5. DISCUSSION

The results do not support the hypothesis that the air pollution variables studied within a metropolitan area affect the pulmonary functions of asthmatic patients. Neither univariate or multivariate regression analyses for individuals and groups identified any consistent effect. In addition, there were no subgroups of asthmatic patients defined according to airways hyperreactivity or the role of reaginic factors in their asthma who appeared to be affected more than others. Failure to identify any systematic relationships ruled out specification of a general model. Importantly, this inability to specify a general model occurred despite elaborate attempts to account for extraneous factors that could influence pulmonary function measurements, including the presence or absence of intraveneous medications at the time of measurement, bronchodilators or treatments taken before measurement, and the previous day's pulmonary function measurement. This paucity of clear results occurred for all spirometric pulmonary function measurements studied, including $FEV_1$, $FEV_1/FVC\%$, and PEFR.

The results must, however, be viewed in relation to the strengths and limitations of the study. There are several notable strengths. First, the study focused upon objective pulmonary function measurements indexing airway obstruction, and studied several of these. This focus is in contrast to

epidemiologic studies (based on clinic and hospital records of treatment) or studies dealing exclusively with subjectively reported breathing difficulties. Second, a well-defined group of asthmatic patients, with moderately severe illness, were studied. Documentation about their asthma was extensive in regard to history, role of allergic (reaginic) factors, and airways hyperreactivity. At each step, analyses proceeded with regard to subclassification based on reaginic factors (thereby minimizing the influence of seasonal airborne pollens upon pulmonary function) and airways hyperreactivity, the degree of which could logically affect the response to air pollution variables in crucial ways. By defining the asthmatic groups in such a detailed way, the study also avoids problems inherent in grouping diverse respiratory illnesses arbitrarily. Third, the final series of analyses considered those factors which could obscure potential relationships between air pollution variables and pulmonary function measures. Using the Clinical Data Management System,[28] it was possible to retrieve not only the pulmonary function data, but permitted verified information about any intraveneous medications or bronchodilator medications and treatments taken before pulmonary function measurement, and the time at which these were taken. These variables, particularly prior bronchodilator treatments, were found to influence pulmonary function measurement importantly. This effect was documented and accounted for within the final series of analyses. Fourth,.two periods of study were selected to maximize the potential impact of all air pollution and meterologic variables. The differences in average levels and variability of the air pollution/meterologic variables contrasted in the expected fashion between the seasonal periods. Finally, the number of available patients within each period was fairly large, providing ample opportunity for any systematic effect of air pollution to be documented.

Nonetheless, the study has a number of real or potential limitations. One potential limitation, regarding the indoor-outdoor air pollution relationships, was more apparent than real. Unlike typical hospitalization, patients at NJHRC are not confined to the building or even the hospital grounds, but are encouraged to move about the Denver area freely - shopping, attending sporting and cultural events or movies - as they would at home. Adolescent patients, for example, continue to walk to school during treatment. The high school is nearly eight blocks away from the hospital. For most patients, therefore, exposure to air pollution should be comparable to people residing at home. Since the study involved retrospective data, no information was available to document time spent outdoors by various patients. Reduced exposure to outdoors on cold days may have limited the relationship between minimum temperature and pulmonary functions in winter. In the Salt Lake City study by Finklea, et al.,[22] there was also indication that reduced exposure on cold days may have influenced the relationship between temperature and attack rates for asthmatics living at home.

Additional information was acquired about the indoor-outdoor air pollution relationships for the patient floors. The patients resided on the second and third floors of a new 10-story building. The intake for the ventilation system of the building drew in outside air at a rate of 180,000 cu ft/min. and provided a minimum of six air exchanges per hour for the building's total volume of 1,800,000 cubic feet. Each patient room had

individual input and exhaust ducts, with additional exhausts located in halls. There are no operating rooms within the hospital and no smoking is permitted on the patient floors or elevators. Research laboratories are located above the patient floors, with each laboratory with any potential for generating fumes provided with hoods over the laboratory areas, and having rooms exhausted at rates exceeding the rest of the building. None of these laboratories are located on the patient floors.

For four days during November, 1976 (November 10 through November 14), a mobile unit from Pedco Environmental Specialists (Cincinnati, Ohio) monitored indoor-outdoor air pollution levels for three patient rooms (two on the third floor and one on the second floor). Examination of this data indicated that for NO, $NO_2$, CO, THC, and $SO_2$ the indoor-outdoor air pollution levels are highly comparable, both in regard to time and absolute magnitude. For $O_3$, which is known to break down rapidly, the indoor levels were consistently near zero despite changes in the outdoor levels. Due to the rapid air exchange in the patient building the time lag was small and on the order of 20 minutes. The unusually high rate of air exchange for the patient building was confirmed by the timed disappearance of tracer gas released in the patient rooms. Additional in-place monitoring of NO and CO described a daily pattern associated with periods of high automobile traffic. Thus, with the exception of $O_3$ and COH, even those patients remaining exclusively within the building would be exposed to CO, $SO_2$, and THC. The absence of an effect of these air pollution variables upon pulmonary functions cannot be attributed to lack of exposure resulting from patient behavior and low indoor-outdoor air pollution relationships.

There are, however, certain real limitations of the study. First, all of these patients were inpatients on around-the-clock bronchodilator regimens, while most were also taking oral corticosteroids either on a daily or alternate day basis. These medication regimens are prescribed to increase the tolerance of patients' airways to irritants capable of aggravating the asthma. Therefore, it is possible that considerable protection was afforded by medications against the adverse affect of air pollution variables. Patients on more minimal medication schedules may therefore be more appropriate to study. Second, only spirometric pulmonary function measurements were used. If the effect of relatively transient changes in air pollution is slight, specific conductance ($SG_{aw}$), or airway resistance ($R_{aw}$) may be preferable indices of airway obstruction.[34] Third, if the effect of air pollution upon asthmatic airways depends upon more prolonged exposure, or if, conversely, the effect is very transient, this study would be expected to fail to document such effects. The study considered only average levels of the air pollution variables for 24 hours preceding pulmonary function measurement. Fourth, these results were limited to the specific air pollution variables studied, as well as the levels achieved during the two seasonal periods. In comparison to the Salt Lake City and New York studies,[22,23] the levels of $SO_2$ were very low: On only one day during the winter period did $SO_2$ achieve a level near 79 $\mu g/m^3$, whereas <u>weekly averages</u> for high exposure patients in the earlier studies occasionally exceeded this level. The levels of $SO_2$ were consistently below levels suggested as producing significant harm in asthmatics.[35] In contrast,

CO levels are generally high, but its effect is principally hematologic and would not be expected to trigger airway obstruction directly by an irritant effect. Related to these considerations, in-place monitoring and indoor-outdoor air pollution monitoring by PEDCO indicated that the highest levels of THC, NO and CO occurred twice daily, near 9:00 am and 6:00 pm. These times of maximum appear to be associated with usual traffic patterns in the area. If the effect is transient, then 8:00 am pulmonary function measurement represents a poor choice. In future studies, pulmonary function measurement should follow times of peak air pollution levels closely.

Finally, the full range of patient medication behavior could not be considered. It is of particular interest that patients often take as-needed (PRN) treatments (usually nebulized bronchodilators) when experiencing breathing difficulty.[35] During periods of high air pollution, more PRNs may be taken and overusage of aerosolized treatments has been related to death in asthma.[37-39] If so, PRN usage may serve to increase pulmonary functions and obscure any direct relationship between air pollution and pulmonary function measurement. By monitoring PRN behavior continuously among nonhospitalized asthmatics, using adapted nebulizers with mini-storage units,[40,41] it may be possible to objectify the impact of air pollution upon this behavior of outpatients.

## 6. RECOMMENDATIONS

This preliminary project has enabled better delineation of the factors which could obscure potential relationships between air pollution variables and airway obstruction in metropolitan, asthmatic populations. Further research should be based on the following recommendations. First, since oral corticosteroid and around-the-clock bronchodilator medications may afford significant protection against the effect of air pollutants, periodically medicated asthmatic patients who are not on these intensive regimens should be studied. Second, if possible, pulmonary function measurements reflecting changes in the large airways, such as airway or total lung resistance, should be used together with spirometric measures. Third, as-needed (PRN) use of aerosolized bronchodilators should be carefully monitored during any study of these patients, since most patients tend to titrate their use of these PRN medications in relation to breathing difficulty. Fourth, in studies of patients not on around-the-clock medications, it would be most desirable to obtain pulmonary function measurements at a time closely following peak daily levels of the air pollution variables. Fifth, lag time for summarizing the air pollution levels should be varied in the analyses, permitting, for example, 8-hour and 24-hour air pollution scores to be related to changes in subsequent pulmonary function measurements, with longer lags also considered. It is not yet known how transient or time dependent any effect of air pollution is upon changes in airway calibre in asthma. Finally, further studies might best be conducted on a prospective basis, permitting stringent control of such factors as medications taken prior to pulmonary function measurement and exposure to the outdoors. It is hoped that the present study has served as a useful model for the development of these future studies.

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